

## **ANNEX 3: Comments of the USPTO**

### **Trilateral Project WM4 Comparative Studies in New Technologies**

#### **Theme: Comparative Study on Examination Practice Relating to Single Nucleotide Polymorphisms (SNPs) and Haplotypes**

##### **EXAMPLE I**

##### **1. Challenges to establishing a complete search, including any considerations regarding the extent to which the full scope of the invention can be searched using automated tools.**

##### **Re: Claim 1**

Claim 1 is drawn to 8 distinct polynucleotide molecules, each of which differs from a parent molecule by a single nucleotide substitution. Prior to conducting a search, the examiner determines whether an election of species or restriction requirement is appropriate if the application is a U.S. nonprovisional application filed under 35 U.S.C. § 111(a), or whether unity of invention is present if the application is the national stage of an international application. When searching for a polynucleotide that contains a SNP within an identified SEQ ID NO., the search includes a search for the identified SEQ ID NO. in addition to a search for the elected polymorphism(s). The databases most frequently searched for NPL disclosing such sequences are the GENBANK, EMBL, SWISSPROT, and PIR sequence databases, as well as commercial databases such as MEDLINE and BIOSIS for text searches. In addition, Derwent's Geneseq and the USPTO's in-house issued patent database are searched for patent documents.

Electronic databases containing nucleotide sequence information often fail to provide searchable indexes of polymorphic nucleic acids. Instead a parent sequence, such as SEQ ID NO: 1, may be present in a searchable listing while information about polymorphic variants are often embedded in the annotation fields of such databases.

If sufficient information (such as gene and/or protein name) is present within a disclosure, a text-based search is usually also performed to search for prior art that relates to sequence variation within a particular gene. However, when found, the data required to support a determination of novelty and non-obviousness is often found within the text or tables of such documents. These are very time intensive to search and analyze.

In addition, there is often little standardization within the prior art for naming or characterizing a particular gene or protein, especially when it is newly or recently discovered. Thus, even in situations where a disclosure identifies a gene/protein name or activity, the prior art may use different terminology and have a different manner of

characterizing any particular gene/protein activity. These differences make it difficult to perform a comprehensive search using textual databases.

Re: Claim 2

In addition to the issues discussed above, a complete search of the prior art relating to any diagnostic applications also requires consideration of whether or not SEQ ID NO: 1 or its variants has been associated with any particular disease. Such a search is best completed using text searching. Any references that are identified using a sequence search must be reviewed individually to determine if a diagnostic application is disclosed.

**2. Challenges faced in comparing the subject matter disclosed in the prior art with the claimed invention.**

Re: Claim 1

In addition to the comments in (1) above, it is noted that polymorphic nucleic acids are often described in terms of alterations or changes at particular positions within a parent reference molecule. However, numbering schemes may differ depending upon whether one is looking at genomic DNA or cDNA. Also, various investigators may choose to use different reference schemes when reporting polymorphic sites. Therefore, it is often difficult to establish a one-to-one correspondence between different disclosures of the same nucleic acids and to disclosures of polymorphic variations.

Re: Claim 2

As long as disease X is specified, there are no additional challenges in comparing the subject matter disclosed in the prior art with that which is claimed other than those specified above as related to Claim 1.

**3. For each example, identify the challenges that are presented in determining whether unity of invention is present either within each claim or between claims both before and after a search has been conducted.**

Re: Claim 1

Pursuant to Annex B of the PCT Administrative Instructions, when a Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature, and thus share a special technical feature, where the following criteria are fulfilled:

- (A) all alternatives have a common property or activity, and

(B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives, or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

The words “significant structural element is shared by all of the alternatives” refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art. The structural element may be a single component or a combination of individual components linked together.

#### Example 1, Claim 1 – Unity *a priori*

Claim 1 is directed to a Markush group of SNPs of SEQ ID NO. 1. In determining whether unity of invention is present, it is first necessary to determine whether all the alternatives have a common property or activity. Here, it is clear from the fact pattern that not all polymorphisms share the same property or activity with respect to disease X. Thus the first challenge is the determination of whether the SNPs share another common property or activity. If the examiner determines that all of the claimed SNPs share a common property of activity, then the examiner must still determine whether a common structure or significant structural element is shared by all of the alternatives. If it were assumed for the purpose of making an *a priori* determination of unity that the parent sequence (SEQ ID NO: 1) is novel and involves an inventive step, then a common structure or element is shared by all of the alternatives.

#### Example 1, Claim 1 – Unity *a posteriori*

SEQ ID NO. 1 is not novel, and does not represent a contribution over the prior art. Thus, even if it was determined *a priori* that the claim had unity of invention, SEQ ID NO. 1 is not sufficient to establish a special technical feature linking the claimed inventions. As noted in the *a priori* analysis above, the first challenge is the determination of whether the polymorphisms share a common property or activity. The fact pattern indicates that polymorphisms 1-3 share a common property with a positive correlation with disease X, and polymorphisms 4-6 may share a common property if they have a negative correlation with disease X. There is no disclosed property or activity shared by any of polymorphisms 7-8. A challenge is presented in determining whether or not a “positive” correlation and a “negative” correlation with the same effect represent a “common” function within the meaning of unity of invention. If so, polymorphisms 1-6 may meet the unity requirement if the polymorphisms also share a common structure or significant structural element. If not, polymorphisms 1-3 would lack unity with polymorphisms 4-6. Polymorphisms 7-8 would lack unity with polymorphisms 1-6 since there is no “common” function within the meaning of unity of invention.

The next challenge is to determine whether polymorphisms that share a common property or activity (e.g., polymorphisms 1-3), also share a common structure or significant structural element. If the novelty of each of polymorphisms 1-3 lies in the specific polymorphic variation, the challenge is in determining whether there would be a significant structural element that would provide unity between the each of polymorphisms 1, 2, and 3. The issue is whether the sequences common to the claimed polymorphic nucleic acids represent a significant structural element that would form the basis of a technical feature within the meaning of, for example, PCT Rule 13.2.

Re: Claim 2

Claims 1 and 2 would be considered to meet the standards for Unity of invention unless the DNA of SEQ ID NO: 1 or its variants was known or if the correlation of the polymorphic variants with disease X was taught in the prior art. Thus, there would likely be an *a priori* finding of unity of invention between claims 1 and 2, even though the separate polymorphic nucleic acids within each claim may be considered to lack unity. Therefore, a single polymorphic nucleic acid and its use would be considered to meet the standards for unity of invention even though each such nucleic acid and its associated method of use may lack unity as discussed above.

**4. For each claim, identify the challenges that are presented regarding the determination of compliance with the clarity, sufficiency (enablement/written description) and industrial applicability/utility requirements.**

Re: Claim 1

Since the claims are clear and the specification provides an adequate written description of the claimed nucleic acid, this example does not present any clarity or written description challenges. Additionally, the specification indicates that polymorphisms 1-3 have been associated with the presence of disease X, thus there is no challenge in determining that polymorphisms 1-3 have a specific, substantial, and credible utility. However, there may be a scope of enablement issue with respect to the use of polymorphisms 4-8 where either a negative correlation or no association to any disease is disclosed and no other utility is disclosed or apparent. Thus the principle challenge posed by Example I is the determination of whether each polymorphism claimed has a specific, substantial, and credibility utility that could be practiced without undue experimentation.

Re: Claim 2

The only specific challenge presented by Claim 2 is whether the claim is enabled over its full scope. Here, there is only a clear positive association between polymorphisms 1-3 and the presence of disease X. Thus absent additional evidence relating to polymorphisms 4-8 it is unlikely that the full scope of the claim is enabled.

## **EXAMPLE II**

### **1. Challenges to establishing a complete search, including any considerations regarding the extent to which the full scope of the invention can be searched using automated tools.**

#### **Re: Claim 1**

This claim presents the same search issues as presented for Claim 1 of Example I above with the caveat that the search for this claim is even more complex because it is necessary to determine the presence of multiple polymorphic nucleotide positions within a single molecule. However, given multiple positions that could be relied upon to distinguish over the prior art, once any particular position within a polymorphism is found to be sufficient to find a given haplotype novel and non-obvious, no further search of any haplotype having the novel and nonobvious polymorphism would be required.

Documentation of the extent of search and reasons for any finding of novelty and non-obvious is essential in situations where a search does not extend to all the polymorphic positions within a given haplotype.

#### **Re: Claim 2**

The same challenges as set forth for Claim 2 of Example I are present when searching a diagnostic method that uses various haplotypes. An additional challenge lies in determining how much patentable weight should be given to step (c), assigning a particular haplotype to an individual based on the results of the claimed nucleic acid comparison, because this claim limitation does not recite any physical process steps. Furthermore, a challenge is presented in determining whether the nucleic acid sequence information being compared in the claimed process would be sufficient to patentably distinguish the claims from a prior art process having the same basic steps, but comparing different nucleic acid sequence information.

### **2. Challenges faced in comparing the subject matter disclosed in the prior art with the claimed invention.**

#### **Re: Claim 1**

The same challenges as set forth above for Example I exist for Example II with the caveat that the level of complexity is greater since multiple polymorphic positions within a single nucleic acid molecule would need to be compared.

#### **Re: Claim 2**

See comments re: Example I, Claim 2 above. Also see the search challenges for Example II, Claim 2, above.

**3. For each example, identify the challenges that are presented in determining whether unity of invention is present either within each claim or between claims both before and after a search has been conducted.**

Re: Claim 1

See comments re Example I, Claim 1. The issue to be resolved is whether there is a common structure and common function that links the various haplotypes claimed.

Re: Claim 2

See comments above for Example I, Claim 2 regarding unity of invention.

**4. For each claim, identify the challenges that are presented regarding the determination of compliance with the clarity, sufficiency (enablement/written description) and industrial applicability/utility requirements.**

Re: Claim 1

The principle challenge posed by Example II is the determination of whether all of the claimed haplotypes have a specific, substantial, and credibility utility that could be practiced without undue experimentation. The description states that the data present in these structures is useful in determining the sensitivity of an individual to drug Y. However, this is a use of the information content of the nucleic acids rather than a use of the nucleic acid *molecules* themselves. A significant challenge exists in determining whether or not the claimed polynucleotides are supported by a specific, substantial, and credible use. The claims are clear, and the specification provides an adequate written description of the claimed subject matter.

Re: Claim 2

The specification does not make an explicit statement asserting a specific, substantial and credible utility for the haplotype assignment method. However, the specification does disclose at least a *potential* use of the claimed molecules (see preceding paragraph) in designing a medical treatment regimen. A challenge is presented in determining whether using the haplotype assignment method as a basis for individualized drug prescription is implicitly disclosed, and if so, whether the data in the specification presents sufficient information to enable one skilled in the art to practice the claimed invention over the full scope of the claims.